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PHENAGLYCODOL THERAPY IN CEREBRAL PALSY

BY

I. NEWTON KUGELMASS

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DEFECTIVE NEUROMUSCULAR CONTROL OF THE CHILD'S VOLUNTARY MOVEMENTS

Clinical Syndromes

Long-term impairment of the involuntary part of voluntary movement is due to reduced flexibility of nervous function. It produces a wide variety of disorders of movement and posture known as cerebral palsy, rather than a unitary state of different degrees of disability. There may be paralysis, weakness, incoordination, or other motor disability affecting manual activity and body ambulation due to a disturbing but nonprogressive lesion in the motor control centers of the brain. The neural mechanism of the affected child is structurally defective. Consequently, acquisition of control of movement is not only delayed but limited in nature and severity according to the extent and situation of this nonprogressive brain lesion, which originates before birth, during delivery, or during postnatal neural maturation. Andersen (1954) found that every type of cerebral palsy affects voluntary activity from the time of its inception, despite residual brain function, in the absence of destroyed components. The evolution of the signs and symptoms of cerebral palsy is thus determined by the systemic effects of the brain lesion upon the child's development.

Neuropathological changes, however, cannot be correlated with the clinical features of all forms of cerebral palsy. The pathological classification of motor aberrations in terms of cerebral involvements is frequently in error because meager, morbid changes may be found in severe cases and, conversely, diffuse changes may be discovered in asymptomatic cases. The current correlation of pyramidal tract involvement with spastics; extrapyramidal or basal nuclei involvement with athetotics, rigidities, and tremors; and cerebellar involvement with ataxics — all are without adequate foundation. The etiological classification is more sound because specific causes frequently are found in certain clinical syndromes with significant correlation, for example, toxemia of pregnancy, in spastic hemiplegia Rh incompatibility in athetosis, prematurity in spastic paraplegia, breech delivery in athetosis, cesarean delivery in rigidity, birth injury in spastic quadriplegia, and anoxia in athetosis.

In the light of our limited knowledge of the diverse mechanisms of cerebral palsy, clinical classification is the most rational of all the systems. The various motor and neurological manifestations usually can be differentiated in terms of spasticity, flaccidity, athetosis, dystonia, rigidity, or tremor. The motor disability may be further differentiated qualitatively in terms of specific site of involvement by paraplegia, diplegia, quadriplegia, hemiplegia, triplegia, and monoplegia. For prognostic value, the degree of severity of involvement is further indicated as mild, moderate, or severe. The degree of muscle tone is expressed as hypertonic or hypotonic. The probable time of occurrence of the brain injury is deduced as prenatal, paranatal, or postnatal. The associated defects are described as part of the total handicap complicated by mental retardation, sensory disturbances, behavior disorders, and convulsive states, since cerebral damage is not limited to a single area in the motor sphere of the cerebral palsy child.

Spastic palsy. This afflication is a generalized disturbance of voluntary movement due to feeble voluntary function of all muscle groups owing to the defect in neural mechanisms. It develops during the first or second year of life, while the associated mental retardation appears earlier, during the fourth month of life. The degrees of motor and mental disability are not necessarily correlated, for severe spastic palsy may impair the activity of a child with normal intelligence, while severe mental deficiency may produce few motor disturbances. Little (1862) observed that spasticity develops gradually as voluntary inaction and postural distortion in the course of maturity. Abnormal inactivity persists throughout the period of motor development. The affected child retains infantile postures; hence rapid passive movement of the limbs evokes the classic sign – a spastic stretch reflex. The more sudden the attempt, the greater the resistance produced; the normal stretch reflex is disturbed both in timing and in strength. The child has difficulty altering positions; the thighs remain adducted and the abductors inactive. Magoun *et al.* (1947) detected the classic neurological signs, that is, increased deep reflexes, positive Babinski, and ankle clonus, irrespective of the degree of spastic involvement.

Athetoid palsy. This is characterized by lack of steadiness of voluntary activity stimulated by the passage of impulses from the cerebral cortex to the final common path. Collis *et al.* (1956) consider the cortical initiation of voluntary movement normal and mental direction of movement unaffected, but disruption of neural activity arises subcortically before the neural impulses from the cortex reach the spinal cord. There is subsequent disturbance in every activity subserved by mechanisms between the cortex and anterior horn cells. All impulses reaching the cord are abnormally distributed, leading to unsteadiness of voluntary movement. Athetotic movements are involuntary, arrhythmic, unwanted, purposeless movements aggravated by voluntary effort and emotional tension, and associated with muscle tension. The hyperkinesis in athetosis does not involve an excess of action, but an excess of fragmentary movements.

Rigidity palsy. This form is due to diffuse brain damage and is characterized by absence of voluntary activity from birth, the muscles being hypertonic and the motion decreased. There is increased resistance to passive motion of both agonist and antagonist muscle, interrupted at regular intervals in a jerky movement in the cogwheel type, or continuous in the lead-pipe type. Variable rigidity may be confused with spasticity because of stiffness, and with athetosis because of ever-changing rigid postures. Rigidity differs from spasticity in the absence of the stretch reflex and the decrease in the irritability and contractility of the muscle response.

Ataxic palsy. The ataxic form is characterized by disturbances of balance, coordination, and control of voluntary movement because of damage to the cerebellum, cerebellar tract, or the eighth cranial nerve. Changes in both the cerebrum and cerebellum are observed in diplegic ataxia, while selective changes in the cerebellum are evident in atonic ataxia. There is failure of the normal involuntary augmentation of tone that accompanies voluntary activity; hence, the movement of the head and trunk to maintain steady posture is imperfect, the movement of the tongue and lips in speech is incongruous, and the movement of the arms and legs is imprecise.

Pathogenetic Determinants

Cerebral palsy may be precipitated by any damage to or disorder of the motor system proper, either genetically, congenitally, paranatally, or postnatally, that is, through the pyramidal system or its subsidaries, the extrapyramidal or cerebellar systems before conception, during pregnancy, at delivery, or in infancy. Denhoff *et al.* (1951) found that the underlying cause of the brain injury and the time of its occurrence in the evolution of the child's development are closely correlated with specific but diverse precipitating factors, pathological changes, and clinical manifestations. This emphasizes the need for a careful history and complete evaluation of the palsied child for rational therapy.

Cerebral hemorrhage in the newborn tends to occur in the large cranial veins and sinuses and in the great vein of Galen adjacent to the precentral gyrus and the motor area, hence the involvement of the pyramidal tract, with ensuing spastic palsy. Submeningeal hemorrhage accompanying birth trauma also tends to involve the pyramidal tract. Cortical hemorrhage tends to occur in precipitate deliveries. Intracerebral hemorrhage tends to accompany maternal hypertensive encephalopathy. Wolf (1951) showed that cerebral anoxia in the newborn is a determining factor in brain damage responsible for athetosis. Despite the high resistance of the neonatal endothelium and hemorrhagic susceptibility, it increases vascular permeability, even in the absence of primary cerebral bleeding. The basal nuclei and their cortical ramifications are more susceptible to anoxia than the pyramidal system, even though the newborn's brain can withstand oxygen deprivation longer than that of the adult.

Prenatal disorders. Prenatal disorders producing motor involvement secondary to brain damage account for 20 per cent of cerebral palsy cases (TABLE 1). Genetic transmission of developmental defects in the pyramidal system causes familial spastic paraplegia; in the basal nuclei and their tracts, atonic diplegia, familial athetosis, congenital tremor, or hereditary rigidity; and in the cerebellum and its tracts, hereditary ataxia. These familial cerebral defects may be accompanied by (1) inborn errors of protein metabolism, for example, phenylpyruvic oligophrenia; (2) carbohydrate metabolism, galactosemia; (3) fat metabolism, gargoylism, Gaucher's disease, Tay-Sachs disease; (4) cellular dysgenesis, for example, tuberous sclerosis, neurofibromatosis, Sturge-Weber disease; and (5) structural defects, for example, craniostenoses, platybasia, porencephaly.

Congenital disorders affecting the fetal brain induce cerebral palsy. Anoxia from interference with placental circulation occurs in maternal hypotension, threatened abortion, placental infarct, premature separation of the placenta, or compression of the umbilical cord. Cerebral hemorrhage in the fetus may be induced by vascular injury, maternal toxemia of pregnancy, maternal eclampsia, blood dyscrasia. Intrauterine infection may cause injury to the fetal brain, especially during the first trimester, by neurotropic viruses, syphilis, or toxoplasmosis. Metabolic disorders, especially diabetes mellitus and hyperthyroidism, may injure the fetal brain. Rh incompatability may injure the basal nuclei and the extrapyramidal system, causing athetotic palsy.

Paranatal disorders. These disorders are responsible for 70 per cent of cerebral palsy as a result of brain injury (TABLE 1). The birth process is accompanied by mechanical injury to the skull and brain, causing laceration of the cortex or hemorrhage into the subdural space or cerebral hemispheres. Oxytocics greatly increase blood flow from the placenta into the fetal circulation. Cerebral hemorrhage also may be induced by hypoprothrombinemia in the newborn or by increased capillary fragility in prematurity, debility, or syphilis. Windle (1950) found that brain injury may be precipitated by anoxia from aspiration of mucus or amniotic fluid, by narcotic depression of the medullary respiratory center, by

TABLE 1

ESTABLISHED CAUSES OF NEUROMUSCULAR DEFECTS IN CEREBRAL PALSY

Prenatal (20%)		*Paranatal (70%)*	*Postnatal (10%)*
Genetic	*Congenital*		
Cellular dysgenesis tuberous sclerosis, neurofibromatosis, Sturge-Weber disease *Enzymic defects* Protein: phenylketonuria Carbohydrate: galactosemia Fat: gargoylism, Gaucher, Tay-Sachs *Structural defects* craniostenoses, platybasia, Arnold-Chiari, diastematomyelia porencephaly, cystic formation absence corpus callosum	*Anoxia* threatened abortion, premature separation placenta, infarcts of placenta *Cerebral hemorrhage* vascular injury, blood dyscrasia, toxemia of pregnancy, eclampsia *Gonadal irradiation* *Maternal infection* neutotropic virus, rubella, mumps, herpes zoster, influenza, syphilis, toxoplasmosis *Metabolic disorders* diabetes, hyperthyroidism *Nutritional deficiency* *Rh incompatibility*	*Anoxia* *Birth injury* *Oxytocics*	*Anoxia* -CO poisoning, hypoglycemia, strangulation *Chemical poisoning* Pb, As, barbiturates, insulin *Degenerative CNS disorders* *Intracranial infections* meningitis, encephalitis, brain abscess, parasitic infiltration, postvaccinial encephalitis, postpertussis encephalitis *Neoplasms* *Trauma* skull fractures, penetrating wounds *Vascular lesions* congenital vascular anomalies, congenital aneurism of circle of Willis, hypertensive encephalopathy, venous thrombosis, vascular lues, endocarditis, sepsis, sickle cell anemia

obstetric anesthesia which causes fetal asphyxia, kinking of the umbilical cord during delivery, prolonged delivery, and placenta previa.

Postnatal disorders. Only 10 per cent of cerebral palsy cases are accounted for by postnatal disorders (TABLE 1). Head trauma may cause skull fractures, with laceration of the motor areas and cerebral hemorrhage. Infections of the central nervous system such as meningitis and encephalitis may produce vascular hemorrhage, with demyelinization of the blood vessels. Perlstein *et al.* (1952) demonstrated that vascular lesions in congenital aneurism of the circle of Willis or hypertensive encephalopathy of renal disease may result in intracerebral hemorrhage, while vascular lesions in endocarditis, sepsis, syphilis, or sickle cell anemia may result in cerebral embolism. Chemical poisoning from lead, arsenic, barbiturates, or insulin may damage the brain and produce cerebral palsy. Anoxia from carbon monoxide poisoning, hypoglycemia, strangulation, or respiratory obstruction may cause brain damage and eventual cerebral palsy. Brain tumors, benign or malignant, may also induce cerebral palsy.

PROGRESS ASSESSMENT OF THERAPY

Assessment of Neuromuscular Criteria

The clinical course of palsied children undergoing various types of treatment simultaneously is difficult to evaluate from the assessments of physicians, therapists, and parents. Each differs in his approach toward the child and each claims favorable results according to his own criteria. Levitt (1957) finds disturbing vagueness in the terminology of recorded progress. The use of comparative terms is questionable, since one examiner's concept of such terms varies considerably from that of another. Comparisons made at periodic intervals by the same examiner are better assessments of progress. The only rational basis for determining the value of any single therapeutic procedure is the periodic evaluation of the child as a whole by objective criteria during the period of specific therapy.

The effectiveness of specific compounds in cerebral palsy is difficult to evaluate quantitatively because of the constant variation in neuromuscular patterns changing from moment to moment in the same individual. Behavior disorders accompanying cerebral palsy usually vary from hour to hour and day to day, hence the degrees of worsening or improvement are always individual, precluding exact correlation with therapeutic measures. Deep tendon reflexes constitute no reliable measure of the degree of spasticity. Electromyograms offer only a comparative guide because the overlying neuromuscular groundwork changes continuously. Even tests of motor efficiency vary with the child's transference to the examiner. The over-all periodic response in palsy is far more revealing clinically than specific day-by-day testing of reflexes and range of motion or other measures of muscular performance. Such meticulous daily evaluation brings to light the enormous fluctuations in response determined by innumerable factors brought to bear upon the child from his internal and external environment. Consequently, functional changes in typical features of cerebral palsy become the clinical criteria for determining the effectiveness of a therapeutic measure.

Physical examination involves movement evaluation (Clark, 1948) and muscle examination (Phelps, 1954) in assessing the child as a whole. The current trend favors movements rather than muscles, since the fundamental pathology in cerebral palsy is predominantly cortical and subcortical. The resultant activity of agonists, antagonists, synergists, and fixators is reflected in movement potential rather than in muscle tone.

Simple movement is tested passively and actively and graded accordingly, and range of joint movement is measured with a goniometer. Range and quality of muscle contractions occurring during voluntary movements performed against resistance are recorded by an ergograph. The range and strength of contractions are graphed subsequently, the muscle work calculated, and the progress evaluations visualized as functional energy. Even these electrographs represent but one phase of cerebral palsy disability. Strength is graded qualitatively in the absence of normal criteria of resistance to a child's movement at different ages. Strength can be measured with the dynamometer, however, and the duration of an activity constitutes a means of determining progress.

The force necessary to overcome the muscle spasticity is measured by the myometer. Periodic photographs reveal progress in posture, balance, and skill, but films present more reliable methods of recording changing activity in cerebral palsy children. Normal movement of any part of the body is determined, not only by the functional integration of the involved muscles and motor complex, but by the functional effectiveness of the total organism reflected in perception, proprioception, kinesthesia, vision, posture, and coordination. Movement disability thus requires careful analysis of balance, coordination, and posture.

Functional tests evaluate the routine activities of everyday life, specific abilities being scored qualitatively and quantitatively. Motor function is correlated with the developmental progress of the child. The motor age test is based on the normal age levels of achievements of motor skills. Electric testing of muscle response enables more accurate assessment of denervated muscles, but the muscles in cerebral palsy show no reaction of degeneration, since the basic lesion is the lack of coordination directed from the brain.

General progress is fully as significant as motor progress. It unravels attitudes toward motor activity, development of speech, display of initiative, improvement in perception, extension of attention span, and response to direction. A social-minded child may show little or no progress in his patterns of defective movement, but considerable improvement in personal aspects of behavior. A lethargic child may learn to socialize with other children, become outgoing, and improve his motor abilities. A verbose child may respond to speech therapy, express himself more effectively, and communicate better with the group. Such personality evaluations transform a palsied child from a collection of defects into an integrated being exhibiting developmental progress.

Assessment of Spastic Criteria

Spastic muscle. This type of muscle is hyperirritable to contraction from any stimulus—tactile, visual, auditory, and emotional—becoming stronger than its antagonist through the multitude of contractions. There is limitation of motion due to an imbalance of opposing muscle groups. The tonic spastic contraction is a clasp-knife rigidity. Spastic muscles do not relax when their antagonists contract, hence the disturbance in posture control. The amount of tonic contraction varies from time to time, being maximal during excitement, when both muscles and their antagonists are affected. The balance of power established between antagonistic muscle groups by treatment increases the range of motion and strength of musculature.

Stretch reflex. This is a diagnostic of spastic muscle. It is elicited mainly in the postural antigravity muscles by a rapid passive stretching of the affected muscle. The muscle is considered spastic if a jerk occurs, that is, a sudden involuntary muscular contraction that checks the attempted passive stretch. The contraction usually extends to contiguous healthy muscles of the same group, producing a mass action movement of the extremity. The stretch reflex is indicated electromyographically by a marked increase in the amplitude and spread of the normal action current of the muscle. The spastic child learns to control the development of the stretch reflex, but his movements are slow because he cannot cope with sudden stimuli. The slowness of muscle contraction may be overcome by repetitive exercises.

Emotional stress. Automatic contraction of the antagonists upon stimulation of a muscle develops emotional stress, either as resentment in the form of anger or as compensation in the form of tractability to the restraint from voluntary movement. Whatever the reaction, the recurring impact of the traumatizing stimulation stirs the inner senses into exaggerated fear of falling, fear of noise, fear of persons, fear of objects. The heightened emotional tension of the spastic accrues from cumulative frustrations in an environment unsuited for his structural or emotional make-up. It induces the general adaptation syndrome as a protective mechanism against cellular injury at the expense of neuromuscular habilitation.

Hyperactivity. This condition is accompanied by impulsiveness, irritability, and short attention span, especially in boys. There is continuous involuntary overactivity after the slightest stimulation, and unpredictable behavior reactions to the simplest experience. Laufer *et al.* (1957) attribute this manifestation of cerebral palsy to diencephalon injury, with consequent sensitivity of the central nervous system to stimuli constantly pouring in from systemic viscera and from peripheral receptors. The mechanism is explicable by the photometrazol electroencephalogram.

Assessment of Athetoid Criteria

Muscle tension. This type of tension is increased during movement and diminished during rest, relaxation, and sleep. The voluntary effort to control irregular movement is transmitted to the musculature as heightened contraction or tension, but contraction of the muscle stimulated to contract by its own nerve impulse cannot be varied in intensity. The loss of voluntary control of the force of contraction leads to incoordination characterized by involuntary minimal or maximal contractions from the same nerve impulse. Tension is usually superimposed on the involuntary motion as a result of the child's effort to counteract this motion by tightening his muscles. The deep reflexes may be increased, but only as a result of superimposed tension. The Babinski sign is negative, but may be thought to be positive if spontaneous movements of the toes coincide with plantar stimulation. Clonus is always absent.

Emotional expression. Continuous tension exercised by the athetoid to accomplish any deed, no matter how trifling, is reflected in emotional expression. The alarm reaction aroused by the physical inadequacy becomes the primary habit pattern of every type of action. Such prolonged states of anxiety and panic toward disorganized inner impulses interfere with developmental progress. However, the athetoid is not too fearful in his overt approach to things but, rather, is skillful in his persistence of impulsive drives, although affectionate in his personal relationships.

Muscular coordination. Failure of the smoothly balanced coordination of agonist and antagonist muscles and overflow innervation of other muscles results in disturbed and disordered muscular coordination. Only in bilateral athetosis are there fatuous facial expressions, writhing movements of the tongue, dysarthria, and dysphagia. This medley of irregularly synchronous contractions of opposing muscular groups leads to no accomplished muscular act.

Body movements. Involuntary, uncontrollable, and uncoordinated body movements are produced against rigidity or tension, and therefore assume bizarre stereotyped patterns. These movements are unwanted, nonrhythmic, and nonrepetitive; they are increased by voluntary effort, diminished at rest, and absent during sleep. Such purposeless body movements appear with voluntary effort, mental exertion, or emotional stress. Attempts to move part of a limb are accompanied by unwanted overflow movements in other limbs and are therefore sudden, brief, and disjointed. Control of involuntary movement can be accomplished best by conscious relaxation, that is, the voluntary ability to master the involuntary contraction of muscle groups. Since the concept of relaxation is difficult to transmit to a child, we must be content with teaching voluntary control of muscle groups.

Postural control. This control is defective, variable, and unpredictable, despite the tendency to repeat certain postural patterns. There is evident in cerebral palsy infants a lack of steadiness of all voluntary activity when they attempt voluntary movement. There is no stiffness, however, until it is added as a result of effort. The head is drawn back, mouth open, tongue protruding, and the forearm is held with palm down and arm drawn back. The characteristic posture of the hand is one of marked flexion of the wrist, with flexion at the metacarpophalangeal and extension at the interphalangeal joints (the posture produced by contraction of the interossei), and the thumb is adducted and extended at the two distal joints. The toes tend to turn up and the foot to turn inward.

CLINICAL EVALUATION OF PHENAGLYCODOL THERAPY

Effectiveness of Drug Therapy

Certain drugs induce muscle relaxation, alleviate disturbing behavior, and control recurrent convulsions in cerebral palsy. They constitute adjuvant therapy rather than substitution for specific modalities, and ameliorate abnormal mechanisms without restoring normal habit patterns or muscle strength. However, they enable the quality of the physical therapy to be improved in the cause of better range of motion and habit-pattern training. Drug therapy is thus more effective in early childhood, especially in preventing muscle imbalance, fixed deformity, and eventual atrophy. Relaxant compounds are formulated early, at the initial establishment of the diagnosis, and are administered for several months in various combinations to facilitate intensive training, physical therapy, and other therapeutic measures.

Muscle relaxants include mephenesin and its analogues, which diminish exaggerated reflexes without altering the physical, developmental, or behavioral spheres. Prenderol, its analogue, further reduces myoclonic seizures and athetoid tensions. Artane diminishes excessive movement, mouth drooling, and digestive disturbances. Neostigmin occasionally relaxes musculature, but always improves gastrointestinal tone in palsied children. Atropine and other sympathomimetic agents relieve cogwheel rigidity and tremors. Dramamine improves balance and coordination. Curare relieves muscle spasm, but its lethal dose is dangerously small and its effective action quite short. Alcohol reduces tension by its action on the cerebral cortex, improving manual activity and body ambulation. Tridione relieves athetosis by its action on the midbrain rather than on the cortex. Strychnine increases muscle tone in hypotonia.

Behavioral regulators include amphetamine sulfate for hyperkinetic motor activity, Benadryl for general physical relaxation, and ataractics for reduced emotional tension. Anticonvulsants are indicated for major or minor seizures accompanying cerebral palsy, although they are less effective in all forms of organic brain disease than in idiopathic epilepsy. Sedatives are indicated in disorders affecting the cerebral palsy child that simulate those encountered in the normal child. Phenobarbital, in doses leading to relaxation, produces either drowsiness or irritability, but Amytal is satisfactory by day and Seconal by night. Chloral hydrate and paraldehyde are more effective than barbiturates in the sedation of the palsied child. There remains a real need for some form of ataractic to buffer the central nervous system from the intense pressures of everyday life.

Assessment of Phenaglycodol Therapy

Phenaglycodol* is the chemical type of central relaxant with the simplest structure and the least toxicity of this group of compounds. It does not alter normal behavior, autonomic functions, or conditioned responses. Berger (1954) found meprobamate, the phenaglycodol analogue, a central nervous system depressant that acts at the level of the spinal cord to induce muscular relaxation. It has other effects at higher levels of the central nervous system, such as relieving tension without causing drowsiness, and it is therefore particularly applicable to the hyperkinetic palsied child. Hendley (1957) demonstrated inhibition of thalamic activity by meprobamate to explain its clinical effects, but the hypothalamus, cerebral cortex, and limbic system, vital in emotional processes, remain unaffected.

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*Phenaglycodol was supplied by Eli Lilly and Company, Indianapolis, Ind., as Ultran.

Our demonstration (Kugelmass, 1956) of the effectiveness of meprobamate in the symptomatic management of organic mental syndromes in the spheres of thought, feeling, and action, and of its superiority over other psychochemotherapeutic agents in mentally retarded children, led us to determine the usefulness of phenaglycodol in cerebral palsy. Several clinical questions arose in approaching this study, for example, the indications, dosage, efficacy, duration, and side effects of phenaglycodol. Previous studies have indicated the favorable effect of meprobamate on the emotional component of the palsied child. Our present study is concerned with the phenaglycodol effect on all clinical aspects of cerebral palsy.

Twenty infants and 24 children, aged 1 to 18 years, under supervision for various types of cerebral palsy and receiving individualized therapy, were given phenaglycodol to determine its effect upon the child as a whole as well as upon his neuromuscular disorder (TABLE 2). There was no possibility of pairing age groups or palsy types in order to obtain parallel studies with controls, for each type of cerebral palsy is a highly individual problem. Control studies had to be made on the same individual by alternating a period of phenaglycodol therapy with an equivalent period on placebo control.

The daily dosage of phenaglycodol ranged from 300 to 3000 mg. in divided doses after meals and at bedtime. Some children showed a desired response on 100 mg. within 30 min. for a period of 5 hours, while others required 3 to 6 times this dosage before any effect was discernible within 120 min. Indeed, the initial hesitancy about offering high dosages because of possible complications led to unwarranted deductions regarding the ineffectiveness of the drug. Then, too, because of the gradual development of adaptation and tolerance to the drug in some children, there was even greater difficulty in establishing the maintenance dose than the primary therapeutic dose. Girls required smaller dosages than boys to produce the same pharmacological effects. Sensitive children required one fourth to one half the general effective dose. The optimal dosage of phenaglycodol was usually attained within a fortnight and maintained for a month or two in order to quantitate motor, emotional, educational, and social progress in each type of palsy.

The active cooperation necessary for effectiveness of all forms of therapy depends far more upon the intellectual capacity than upon the motor defect, hence the intelligence rating was determined for the entire group of palsied children (TABLE 3). The mild palsies, comprising 50 per cent, were given the Stanford-Binet form L and Cattell infant intelligence tests. The moderate palsies, comprising 30 per cent, were given the modified Stanford-Binet test and the Columbia mental maturity test adapted to the individual child. The severe palsies, comprising

TABLE 2

PERCENTAGE DISTRIBUTION OF DEVELOPMENTAL DEVIATIONS IN CEREBRAL PALSY, 44 CASES

Type	*Developmental retardation*	*Mental retardation*	*Visuomotor defect*	*Visual defect*
Spastic	85	60	30	25
Athetoid	75	50	5	12

Type	*Hearing defect*	*Speech defect*	*Emotional disturbance*	*Behavior disturbance*	*Convulsive disorder*
Spastic	5	50	90	85	35
Athetoid	20	90	80	70	15

20 per cent, were not amenable to any testing procedures. About 20 per cent showed an I.Q. less than 40; 45 per cent between 40 and 70; 30 per cent between 70 and 100; and 5 per cent exceeded 100 (TABLE 4). There was no appreciable I.Q. difference between spastics and athetoids, although 30 per cent of the former and only 5 per cent of the latter showed visuomotor disturbances.

TABLE 3

PSYCHOMETRIC TESTS FOR PALSIED CHILDREN

Degree of palsy	*Per cent*	*Test*
Mild	50	Stanford-Binet, L Cattell infant tests
Moderate	30	Stanford-Binet Modified Columbia mental tests
Severe	20	

The two predominant groups, the spastic and athetoid, composed the entire series of palsied children, with a rare case of rigidity, ataxia, or tremor, for complete assessment in the phenaglycodol study. The spastic group revealed functional improvement in several clinical criteria, that is, the spastic muscle improved in 35 per cent, the stretch reflex in 35 per cent, emotional stress in 30 per cent, and hyperactivity in 25 per cent of the cases (FIGURE 1). The spastic children responded to phenaglycodol in specific aspects, clearly delineated by comparative studies at periodic intervals. There was some improvement in restraint of volitional attempts in 8 children, and a diminution in the violent reaction to sudden loud noise in 14 children. Muscle stiffening diminished somewhat in most of the children; the deep tendon reflexes showed some loss of hyperactivity in 12 children. Muscle clonus was marked in 8 children after quick stretch. Overflow movements diminished substantially in 18 children, reflected in diminished manifestations of facial contortions, compression of the lips, and production of guttural sounds, and in increased respiration or hyperextension of the legs. Spastic children also showed greater cooperation and more improvement in their response to physical therapy during phenaglycodol therapy than during the control period. Apprehension was diminished in all children. Balance improved in 18 children, standing posture in 12, weight transference in 10, and correct falling in 8 children.

TABLE 4

INTELLIGENCE RATING OF THE PALSIED CHILDREN

I. Q.	*Per cent*
>100	5
70-100	30
40-70	45
<40	20

The athetoid group showed greater responsiveness to adjuvant phenaglycodol therapy than the spastic group. Muscle tension improved in 50 per cent of the cases, emotional expression in 40 per cent, muscle coordination in 30 per cent, body movements in 25 per cent, and postural control in 20 per cent (FIGURE 2). Athetoid children showed marked improvement in neuromuscular disturbances; that is, overflow movements were diminished in 18 children, irregular movements in 8, fatuous facial expressions in 12, abnormal posturing in 8, and stiffening spells in 2. There was an over-all decrease in involuntary motion without alteration of voluntary motion. However, no change was observed in 4 children with the calm type of athetosis maintained on this drug. Athetoids responded to physical therapy regimen far better during phenaglycodol therapy than during the control period (TABLE 5). Better range of motion and habit pattern training were obtained in the younger than in the older palsied group. Body relaxation in the sitting and lying positions improved in most of the children. Head balance improved in 14 children; trunk control in 10, sitting balance in 10, and finger painting in 4; all improved in both form and function for longer periods (TABLE 6).

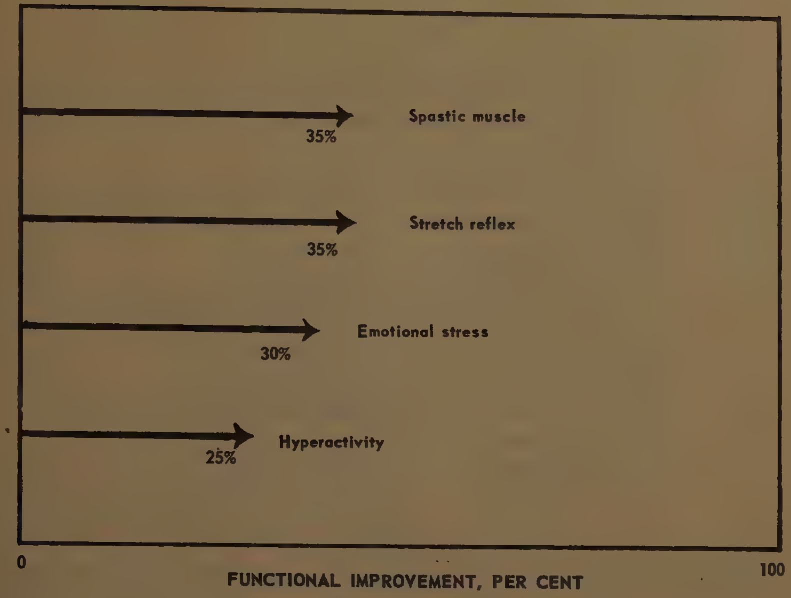

FIGURE 1. Spastic palsy.

Physical training programs originally were difficult in spastics and athetoids with relatively normal or somewhat subnormal mentality, not because of basic incapacity to learn or cooperate, but because of the disabling effect of intense emotionality, continuous fear, and unsuccessful effort. Adjuvant phenaglycodol therapy alleviated the emotionality and fear, but not the incapacity or inefficiency, far more in the athetoids than in the spastics. Actual fears were not relieved, but the intensity of the fears and the paralysis of the action evoked by them were alleviated by phenaglycodol. The body frame of most athetoids, tremulous at intervals with nervous agitation, settled in repose throughout the day's guided activities. The increased calm was not an end in itself, but it served to help the athetoid acquire better coordination of his motor skills.

Personality studies of the spastics and athetoids revealed more feelings of anxiety and frustration than of conflict and hostility, the accumulated emotional tension dissipating into disturbed motor activity. There was marked emotional maladjustment to their disabilities because of ambivalent attitudes toward themselves and poor relationships with their families, consisting of conflicting attitudes toward them. Educational programs designed to lead each family group into more harmonious relationships with the palsied child were more effective during phenaglycodol therapy than during the placebo period. Persistent emotional disorders in the older palsy patient required psychotherapy.

TABLE 5

INDIRECT IMPROVEMENT ON PHENAGLYCODOL THERAPY
(GREATER IN ATHETOIDS THAN SPASTICS)

Athetoids	*Spastics*
Abnormal posturing	Emotional stress
Body movements	Facial contortions
Emotional expression	Fear of falling
Facial grimaces	Guttural sounds
Involuntary motion	Hyperactivity
Irregular movements	Lip compression
Muscle coordination	Muscle stiffening
Muscle tension	Noise sensitivity
Overflow movements	Spastic muscle
Postural control	Stretch reflex
Stiffening spells	Volitional attempts

Both groups of palsied children, athetoids more than spastics, improved in the caliber of their performance in daily routine activities—cooperating in feeding and drinking, dressing and undressing, bladder and bowel training—during phenaglycodol administration, and reverted to variable extents during placebo maintenance. There was definite nutritional improvement, correlated with greater relaxation and longer sleep periods in 30 per cent of the palsied children in comparison with inappreciable changes in the nutritional status during placebo periods. Feeding difficulties were relieved to some extent. Sucking improved in 12 children, chewing in 8, swallowing in 8; there was less choking in 6, less gagging in 2, and vomiting cleared completely in 8. Speech disorders, in about 80 per cent of the children, were relieved only to a very minor degree by phenaglycodol; that is, breathing discoordination improved slightly in 8 children, chewing in 6, sucking in 6, swallowing in 6, and stuttering in 1. Parents were more impressed by the positive changes in emotional behavior and motor function than the therapists.

Assessment of Adverse Phenaglycodol Effects

Phenaglycodol showed a wide margin of safety, with few side effects or significant complications on any dosage; these were more evident to the examiner than to the child. The physical side effects were more conspicuous than the emotional complications. Nevertheless, there was safety in phenaglycodol for prolonged therapy. It was well tolerated, relatively nontoxic, and nonproductive of blood dyscrasia. There was added protection in the complete physical and mental examination of the cerebral palsy child at periodic intervals, and complete medical surveillance for physical and mental symptoms during drug therapy.

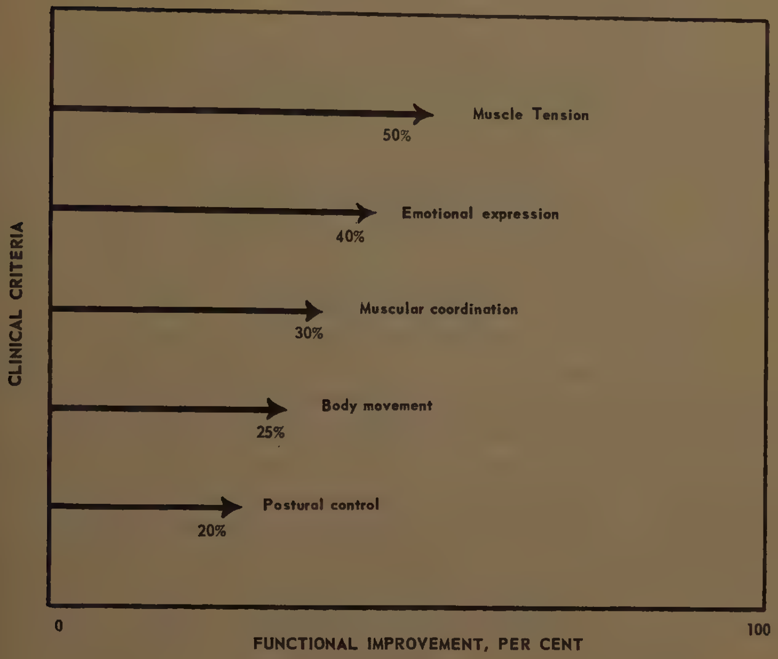

FIGURE 2. Athetoid palsy.

Gastrointestinal disorders occurred in 3 cases, with mild but well-defined reactions, that is, mouth burning, nausea, abdominal pain, or transient diarrhea. Emotional disorders developed in 2 cases, manifested by excitement or depression in a younger child and by headache and irritability in an older child. Prolonged excitation and increased anxiety occurred in 1 child receiving doses of 1500 to 3000 mg./day. Locomotor difficulties with dizziness developed in 1 child maintained on 1000 mg./day for 4 months. Parkinsonism developed within 48 hours in 1 cerebral palsy child with *petit mal* who was maintained on 1000 mg. meprobamate/day, probably due to overstimulation of the extrapyramidal system. There was muscular rigidity, with cogwheel phenomenon, slowing of movement, loss of associated movements, and festinating gait, but all manifestations were reversed with discontinuance of the drug (TABLE 7).

Allergic reactions were not anticipated from phenaglycodol because of its chemical structure. Nevertheless, 2 children of allergic constitution and 2 children with no previous personal or family history of allergy developed cutaneous manifestations with local erythema, intense itching, macular urticaria, angioedema, and allergic purpura. Arthralgia occurred in 1 of the 2 children with angioedema, localizing in the knees and

TABLE 6

PHYSIOTHERAPY PROGRESS ON PHENAGLYCODOL THERAPY

Athetoids	*Spastics*
Body relaxation	Apprehension
Finger painting	Body balance
Head balance	Correct falling
Sitting balance	Standing posture
Trunk control	Weight transference

ankles. Allergic purpura appeared in 1 child who had eczema in infancy. The tourniquet test was positive, but bleeding time and platelet counts were normal, indicating vascular injury. Clinical toxicity of phenaglycodol was slight, since a palsied child 11 years of age ingested 8 gm. without untoward effects other than excessive drowsiness for the afternoon. Hyperactive palsied children who required maximal dosages of 3 gm./day for desirable effects showed persistent hypotension.

TABLE 7

ADVERSE EFFECTS OF PHENAGLYCODOL THERAPY

Gastrointestinal (7 per cent)	*Allergic (8 per cent)*	*Cerebral (9 per cent)*
Abdominal pain	Angioedema	Depression
Canker sore	Erythema	Dizziness
Mouth burning	Itching	Excitement
Nausea	Purpura	Headache
Transient diarrhea	Urticaria	Parkinsonism

SUMMARY

(1) Defective neuromuscular control of the child's voluntary movements is evaluated in terms of the five established clinical syndromes.

(2) Pathogenetic determinants of cerebral palsy are enumerated according to the time of the brain damage in the evolution of the child—prenatal, paranatal, or postnatal.

(3) Clinical characteristics, both mild and severe, of the five types of cerebral palsy infants and children are enumerated to enhance their clarity for early diagnosis and differentiation.

(4) Team management of cerebral palsy combines the current advantages of the clinical practice of medical supervision, orthopedic care, physical therapy, and psychological training.

(5) Progress assessment of specific therapy is evaluated in terms of neuromuscular criteria for each type of cerebral palsy.

(6) The administration of phenaglycodol was found to be a valuable adjuvant therapy in 20 infants and 24 children with cerebral palsy; in a dosage of 450 mg. for infants and 900 mg. for children, it was more effective in the athetoid than in the spastic type, with a range of 300 to 3000 mg./day adapted to individual requirements.

(7) Mild palsies, comprising 50 per cent of the group, and moderate palsies, comprising 20 per cent, amenable to psychometric testing showed 5 per cent with I.Q.s above 100, 30 per cent between 70 and 100, 45 per cent between 40 and 70, and 20 per cent less than 40.

(8) In the athetoid group on phenaglycodol, about one half of the children showed greater relaxation in muscle and emotional tension, and one fourth showed improvement in posture and movement. Some improved in overflow movements. Almost all cooperated more in their physiotherapy regimen, with consequent improvement in attitude and activity.

(9) In the spastic group on phenaglycodol, about one third of the children showed greater relaxation in muscle spasticity and emotional tension, and one fourth showed improvement in hyperactivity. Some improved in their fear of falling, reaction to sudden loud noise, and overflow movements, and most cooperated in physical therapy regimens, with consequent improvement in posture and movement.

(10) Phenaglycodol showed a wide margin of safety with massive doses, but precipitated adverse gastrointestinal reactions in 7 per cent, allergic in 8 per cent, and cerebral in 9 per cent of the 44 palsied children studied.

REFERENCES

ANDERSEN, B. 1954. J. Oslo City Hosps. **4**: 65.

BERGER, F. M. 1954. J. Pharmacol. Exptl. Therap. **112**: 413.

CLARK, G. 1948. Brain. **71**: 320.

COLLIS, E., W. R. F. COLLIS, W. DUNHAM, L. T. HILLARD & D. LAWSON. 1953. Public Health Repts. U. S. **66**: 168. *Also* Infantile Cerebral Palsies. 1956. Heinemann. London, England.

DENHOFF, E., V. N. SMIRNOFF & R. H. HOLDEN. 1951. New Engl. J. Med. **245**: 728.

HENDLEY, C. D., T. E. LYNES & F. M. BERGER. 1957. Symposium. Tranquilizing drugs. Am. Assoc. Advance. Sci. Publ. **46**.

KUGELMASS, I. N. 1955. Mental Deficiency in Infancy and Childhood. Grune & Stratton. New York, N. Y.

KUGELMASS, I. N. 1956. Intern. Record Med. **169**: 323.

LAUFER, M. W., E. DENHOFF & G. SOLOMONS. 1957. Psychosomat. Med. **19**: 38.

LEVITT, S. 1957. Brit. J. Phys. Med. **20**: 127.

LITTLE, W. J. 1862. Trans. Obstet. Soc. London. **3**: 293.

MAGOUN, H. W. & R. RHINES. 1947. Spasticity. The Stretch-Reflex and Extrapyramidal Systems. Thomas. Springfield, Ill.

PERLSTEIN, M. A. & H. E. BARNETT. 1952. J. Am. Med. Assoc. **148**: 1389.
PHELPS, W. M. 1954. Cerebral Palsy. Children's Rehabilitation Inst. Baltimore, Md.
WINDLE, W. F. 1950. Asphyxia Neonatorum. Thomas. Springfield, Ill.
WOLF, A. 1951. Quart. Rev. Pediat. **6**: 104.

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